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Newer Viruses

WILLIAM S. JORDAN

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MONTHLY CLINICAL MONOGRAPHS ON CURRENT MEDICAL PROBLEMS

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Newer Viruses

WILLIAM S. JORDAN

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William S. Jordan

joined the faculty of the University of Virginia in 1958 as Professor of Preventive Medicine and Professor of Medicine, and Chairman of the Department of Preventive Medicine. During the preceding 10 years, he collaborated with the members of the Department of Preventive Medicine at Western Reserve University in a study of illness in a group of Cleveland families. Data from this study emphasized the frequency of occurrence of virus infections, particularly those responsible for respiratory and gastrointestinal symptoms. Dr. Jordan's recent contributions deal with the epidemiology of influenza and adenovirus infections.

MORE THAN 80 human viruses have been discovered in the past 12 years. This fact stands as a tribute and a challenge to the many investigators who have so successfully utilized new hosts and new technics for the propagation of viruses (20). The use of newborn mice by Dalldorf and Sickles led to the discovery of the Coxsackie viruses; the use of cells maintained in tissue culture systems permitted isolation of the ECHO viruses, the adenoviruses and many others. Some of these agents were promptly related to specific illnesses; others, initially classified as "orphans," gradually have been associated with a variety of syndromes; still others remain "viruses in search of disease" (11, 22).

The illnesses produced by these new viruses are many and varied, with clinical manifestations ranging from coryza to paralysis, from myalgia to myocarditis. Most of the agents have been classified in two main groups—the enteroviruses and the adenoviruses. Although the former are found primarily in the intestinal tract and the latter in the respiratory tract, these groups have many epidemiologic features in common. The following general characteristics, while not applicable to every type, are descriptive of the behavior of both the adenoviruses and the enteroviruses:

1. Their distribution is world-wide.
2. They are spread by person-to-person contact.
3. They produce both epidemic and sporadic infections.

4. Many infections are clinically inapparent.

5. They produce minor, undifferentiated febrile illnesses as well as characteristic clinical entities.

6. With a proper combination of factors, the most important of which currently appears to be the susceptibility of infants, certain types produce fatal disease.

7. Infection and illness are more common in childhood.

8. A significantly higher percentage of adults than children have antibodies against each virus type.

9. Adults tend to have antibodies against more virus types than children, reflecting multiple infections throughout childhood and adolescence.

10. Diagnostic procedures are time consuming, and the results often will not be available until the patient is convalescing. Virus isolation is the surest and most rapid way of confirming the diagnosis, but may not be conclusive, particularly in sporadic cases, because of the high frequency of carriers of certain of these viruses. Antibody increases are confirmatory, but because of the multiplicity of types, serologic studies are often impractical. During the acute stage of the illness, the physician must rely on the epidemiologic features and the clinical signs and symptoms in making a diagnosis.

ENTEROVIRUSES

Two groups of viruses, Coxsackie (10) and ECHO (9) were discovered as a by-product of testing fecal samples for the presence of polioviruses. Because of the similarities between members of these two groups and the polioviruses, the three families have recently been joined to form the Enterovirus group. There is considerable overlap of the biologic characteristics of the subgroups. Coxsackie viruses produce disease in suckling mice; Coxsackie Group A viruses destroy striated muscle and cause flaccid paralysis; Coxsackie Group B viruses produce lesions in other tissues and organs, including the brain and cardiac muscle, as well as in voluntary muscle. Twenty-nine antigenic types have been recognized, 24 Group A and 5 Group B.

ECHO viruses (enteric cytopathogenic human orphan) grow in tissue culture, and initially were separated from Coxsackie viruses because they were not pathogenic for infant mice. However, strains of ECHO 9 and 10 viruses have been shown to induce lesions in infant mice like those produced by Coxsackie A and B vi-

TABLE 1.—ENTEROVIRUSES AND DISEASE*

VIRUSES	TYPES	ASSOCIATED DISEASE
Polioviruses (3)	1, 2, 3	Undifferentiated febrile illness
	1, 2, 3	Aseptic meningitis
	1, 2, 3	Paralysis
Coxsackie viruses (29)		
	Multiple	Undifferentiated febrile illness
	2, 4, 5, 6, 8, 10	Herpangina
A (24)	9, 16	Exanthem
	7 and 9	Aseptic meningitis
	7	Paralysis
	1, 2, 3, 4, 5	Undifferentiated febrile illness
	1 and 3; 2 (?)	Pleurodynia
B (5)	1, 2, 3, 4, 5	Aseptic meningitis
	(?) 2, 3, 4, 5	Paralysis
	2, 3, 4, 5	Myocarditis of newborn
	(?) 1, 3, 4, 5	Pericarditis (?)
ECHO viruses (24)	Multiple	Undifferentiated febrile illness
	2, 4, 6, *9*, 14, *16*	Exanthem
	2, 3, *4*, 5, *6*, 7, *9*, 14, 16, 17	Aseptic meningitis
	2, 4, 6, 9	Paralysis
	2, 6, 7, 8, 10, 11, 12, 14, *18*, 19	Summer diarrhea of infants
	(?) 10, 11, and 20	Upper respiratory illness (?)

*The types listed have all been associated with the disease shown, but etiologic relationships have not been conclusively established in all instances. ECHO types most often or convincingly related to a particular manifestation are in italics.

ruses, respectively. Further, Coxsackie B viruses and some Coxsackie A strains grow in tissue culture cells and may not be pathogenic for infant mice on primary isolation. Finally, certain strains of these two groups, Coxsackie A7 and ECHO 9, produce neuronal lesions in monkeys similar to those produced by polioviruses. Coxsackie and ECHO viruses differ from polioviruses in that they are easily isolated from the spinal fluid of patients with aseptic meningitis. To date, 24 ECHO viruses have been typed, and oth-

ers await classification. Table 1 summarizes the association of enteroviruses with human disease. In many instances, the etiologic relationship of virus to disease has been clearly shown; in others, the evidence is suggestive but not conclusive. The clinical manifestations listed are considered in the next two sections.

COXSACKIE VIRUS DISEASES

Herpangina

Group A viruses now have been regularly and repeatedly associated with the distinctive clinical features of herpangina. In the combined experience of investigators throughout the world, Group A Coxsackie viruses have been isolated from 75% of cases. Six Group A strains have been isolated from cases of herpangina in different parts of the United States. In the summer months, one or more of these strains has been found in as many as 10% of children attending pediatric clinics. Despite the widespread distribution of these agents, the consistency with which they have been found in typical cases coupled with concurrent serologic responses has established their etiologic role in herpangina. During the rapid spread of A viruses through a household or community, about one third of those infected develop the clinical picture, complete with faucial lesions, originally reported by Zahorsky. Other individuals experience the nonspecific symptoms of fever, anorexia, malaise and sore throat without manifesting the typical phargyngeal vesicles. Many (40-50%) have no symptoms.

In a typical case, the onset is abrupt, with an elevation of temperature (102-105 F.), frequent vomiting and, in young children, even convulsions. Headache, malaise and anorexia are common and may be accompanied by abdominal pain and myalgia involving neck and extremities. Children old enough to do so, complain of a mild sore throat; dysphagia may occur. The characteristic lesions of this entity are located on the anterior pillars of the fauces and soft palate. Early in the illness, only minute petechiae, papules or white or gray vesicles may be seen at these sites. By the second or third day, small superficial ulcers surrounded by red areolæ have evolved. These 1 to 3 mm. lesions are generally few in number and limited to the anterior pillars, but may appear else-

where on the oral mucosa and tongue. There is no adenitis. The leukocyte count is normal.

By the time the ulcerations are evident, the patient has begun to feel better; by the fourth day, even before the lesions have healed, the child is asymptomatic. The disease runs a mild, self-limited course. Until recently, no complications had been reported. In 1955, Howlett, Somlo and Katz isolated Group A (types not reported) Coxsackie viruses from adults with herpetiform mouth lesions and parotitis. Two of the patients also developed gingivitis. Herpes simplex virus was not isolated; there was no increase in titer of mumps antibody. Accordingly, the cases were considered to represent herpangina with parotitis. Antibody responses to the Coxsackie strains isolated were not reported. Parotid swelling or tenderness has not been observed in children with herpangina, and additional data are necessary to establish Coxsackie A viruses as another cause of parotitis.

In the summer of 1957, an outbreak of illness related to Coxsackie A16 occurred in Toronto. The characteristic feature of the illness was the presence of a maculopapular or vesicular exanthem associated with pharyngeal lesions. The faucial lesions resembled herpangina, but the gums and tongue were also involved. As noted below, a rash has been seen with other Coxsackie A infections; it is an uncommon feature of herpangina.

Pleurodynia

Like herpangina, the clinical manifestations of epidemic pleurodynia are characteristic enough to have permitted its recognition as an entity long before the identification of Group B Coxsackie viruses as etiologic agents. The various names for the disease reflect its manifestations and history. The occurrence of multiple cases with severe paroxysmal pain in the region of the attachment of the diaphragm (pleurodynia), or diffuse thoracic and abdominal pain (myalgia), gave rise to the names "epidemic pleurodynia" and "epidemic myalgia." "Devil's grip" connotes the startling suddenness of the occurrence and recurrence of the pain. First observed in Iceland and reported in Norway, the disease

was extensively observed during an outbreak on the island of Bornholm, and has been referred to as "Bornholm disease."

Of the five B viruses, only types 1 and 3 have been definitely confirmed as etiologic agents; type 2 was isolated from a single case during a recent epidemic in Adelaide, Australia, but this type could not be definitely related to the other cases. Like herpangina, epidemics of pleurodynia occur in the summer and fall. Many more adults are involved, presumably a reflection of the lesser prevalence of Coxsackie B infections in childhood.

After an incubation period of 3-5 days, the disease begins suddenly with pain in the chest or abdomen. When extreme, the pain is frightening, is aggravated by respiration or motion and causes the patient to clasp his chest, to lean forward and to breathe shallowly and rapidly. There is associated fever, headache and fatigability. Some patients complain of a sore throat; some have vertigo. Nausea and vomiting may occur in young children. As promptly as it started, the pain may stop only to return again a short time later. The fever, too, may be intermittent, recurring during the exacerbations of pain. Not all patients have such typical or such well-localized pain; some complain only of a generalized ache throughout the back and chest. Examination is of little help. The patient is observed to be apprehensive and restless. The affected area may show some tenderness and hyperesthesia. Pleural and pleuropericardial friction rubs have been reported. Roentgenograms show no pulmonary involvement. The leukocyte count is normal. Sporadic cases may easily be confused with pleurisy, biliary colic, myocardial infarction, pericarditis, appendicitis, etc. Once an epidemic has been recognized, the clinical diagnosis is much more obvious.

Even with severe symptoms, the disease is usually benign and self-limited. Symptoms may last for a few days or, with recurrences, for 3-4 weeks. Most patients recover without complications, although orchitis or meningitis are not uncommon. These complications, certainly the meningitis, might more properly be classed as concurrent manifestations of Group B infection. An association between pleurodynia and aseptic meningitis, suggesting a common etiology, has been noted for a number of years, and prompted the use of the term *meningitis myalgica*.

Aseptic Meningitis

The meaning of the term "aseptic meningitis" has evolved since it was originally introduced by Wallgren to designate a specific entity. By common usage, it now refers to a syndrome characterized by the signs and symptoms of meningeal irritation in which the spinal fluid is sterile by the usual bacteriologic technics and contains an increased number of cells, predominantly lymphocytes. Although many infectious and noninfectious agents may produce lymphocytic meningitis, most such cases are due to virus infections. During the past 10 years, it has been demonstrated that both Coxsackie and ECHO (see below) viruses, as well as the first of the enteroviruses, poliomyelitis, are important etiologic agents in aseptic meningitis.

The association of Group B, type 1 viruses with an epidemic of aseptic meningitis in Connecticut and Rhode Island in 1948 was soon followed by the isolation of Coxsackie viruses from similar patients throughout the United States, Canada, Europe and South Africa. B4 virus was recovered from patients in Massachusetts the next year. B1 and B2 viruses were related to illnesses in Ontario in 1950 and 1951. B3 infections were documented in Australia. In 1952, B4 virus was isolated from the stools of 13 of 33 children with "nonparalytic poliomyelitis" in Toronto. The same virus was recovered from the cerebrospinal fluid of 3 patients. In 1953, B2 virus was isolated during an outbreak in an institution for mental defectives in Philadelphia. In 1954, types B2 and B4 produced meningitis in young adults in Seattle. In 1955–56 in Connecticut, types B2, B3 and B4 were isolated from patients and, in addition, a Coxsackie virus classified in Group A was incriminated as a cause of aseptic meningitis. Coxsackie A9 virus was isolated from the spinal fluid of 2 patients. Because Coxsackie A strains of this type will produce cytopathogenic effects in tissue culture, A9 virus actually had been isolated several years earlier when viruses from patients with poliomyelitis were first being grown in tissue culture. At least one other Coxsackie A virus—type 7—also produces aseptic meningitis. Coxsackie viruses, particularly Group B, are now considered one of the commonest identifiable causes of aseptic meningitis. B viruses have been isolated from 7-19% of cases in various series in Can-

ada, Sweden and the United States. At times, B viruses may be responsible for nearly all the cases.

The epidemic occurrence of infection with B5 virus in the middle western section of the United States in the summer and fall of 1956 is an example of this. In the Minnesota outbreak, B5 virus was isolated from 61 patients. Serologic studies confirmed infection with B5 virus and excluded concomitant poliovirus infection. Rubin and associates (21) estimated that in Cerro Gordo County, Iowa, not far from the location of cases in southern Minnesota, there was an over-all clinical attack rate of 8% during the 12 weeks of the epidemic. There was a broad spectrum of illness ranging from minor symptoms to the manifestations of aseptic meningitis. Attack rates were highest in the younger age groups; the secondary clinical attack rate in families of reported cases was 15%. The secondary subclinical attack rate was much higher, for 66% of the members of 19 families gave evidence of infection with B5 virus. The nonmeningeal minor illnesses followed the same epidemic pattern as did the meningeal ones. The age distribution of cases of minor illness and of aseptic meningitis were similar. B5 virus was isolated from 66% of patients with meningitis, from 61% of patients with minor illness, from 41% of well family contacts and from 30% of well "control" patients. The high rate of inapparent infection in families with cases and the frequent isolation of virus from asymptomatic "control" families indicates that certain B viruses may be as widely distributed in the community during an epidemic as the A viruses of herpangina and, like A viruses, B viruses cause a minor illness characterized by low-grade fever, headache, mild sore throat, myalgia, nausea and occasionally vomiting which, in sporadic cases, is clinically indistinguishable from infections produced by a variety of agents. In reference to the relationship of Coxsackie B viruses to both pleurodynia and aseptic meningitis and of the two major clinical expressions to one another, only 19% of patients 20 years of age and over complained of pleuritic pain.

In the absence of pleurodynia, there are no clinical features which differentiate aseptic meningitis caused by Coxsackie viruses (A7 and 9; B1-5) from that caused by the other enteroviruses. As in pleurodynia, the incubation period is 3-5 days. The onset is sudden, with fever, severe headache, stiff neck, stiff back and leg

pains. Prodromal constitutional symptoms of fever, malaise and cramping abdominal pain may precede those indicative of meningeal irritation. In some instances, rather than merging into the major phase, the prodromal symptoms may be followed by an asymptomatic apyrexial phase producing a diphasic course similar to that manifest by some patients with poliomyelitis. Gastrointestinal symptoms—anorexia, nausea, vomiting and abdominal pain —are common. Other symptoms noted include drowsiness, dizziness, weakness, generalized aches and sore throat. Diarrhea is uncommon and there is no urinary retention.

The physical findings are those of meningitis and are not distinctive. Temperatures range from 99 to 105 F.; the usual admission temperature falls to between 102 and 103 F. The pulse rate is correspondingly increased. Respiratory rates are normal. There is stiffness of the neck or back, and even spasm of the hamstring muscles. In the absence of progressive central nervous system involvement (see below) the reflexes remain normal, there is no muscular tremor and weakness is transient. Hyperemia of the pharynx is mild and of short duration. Despite the abdominal pain, no definite abnormal signs have been described. The total leukocyte count of the blood is usually normal, although a number of elevations to 15,000 have been reported. Cerebrospinal fluid cell counts usually range from 100 to 500 cells. Many polymorphonuclear cells may be observed when the spinal tap is done early in the illness. Later, lymphocytes predominate, and the protein may become slightly elevated. Sugar and chloride values are normal.

The duration of illness ranges from a few days to 3 weeks. Most patients can be discharged from the hospital in 7-10 days.

Paralytic Disease

The frequency with which Coxsackie viruses, particularly Group A, are isolated from children in good health or with minor illnesses makes their presence in cases clinically indistinguishable from paralytic poliomyelitis difficult to evaluate. Although a Coxsackie strain alone is isolated from the stool, there is always the possibility that poliovirus was responsible for the paralysis. Indeed, this was the general interpretation with reference to the isolation

of the initial Coxsackie strains from 2 patients with paralytic disease. Subsequently, Coxsackie viruses have been recovered from other paralytic patients, and immunologic studies have shown an increase in titer of antibodies for the infecting virus but not for any of the 3 types of poliovirus. Such temporal relationships, the exclusion of poliovirus infection and, finally, the demonstration that certain Coxsackie strains produce lesions in the central nervous system of monkeys which are indistinguishable from those caused by poliovirus provide strong evidence for the etiologic role of Coxsackie virus in paralytic disease.

In 1952, Chumakov *et al.* recovered a virus from Russian children with clinical illnesses characteristic of paralytic poliomyelitis, including 2 with fatal bulbar disease. Because the agent produced paralytic disease in monkeys but was not neutralized by antisera against types 1, 2 or 3 polioviruses, it was designated as "type 4 poliovirus." This virus has been shown to be identical with Coxsackie A7 virus, and its neurogenic properties confirmed by several investigators. A7 strains isolated in the United States similarly have been shown to be capable of producing polio-like lesions in monkeys. Steigman (23) recently reported the first laboratory-confirmed Coxsackie A7 infection in the United States associated with the clinical picture of paralytic poliomyelitis. A 3-year-old boy was hospitalized in 1956 with an acute febrile illness and signs of meningeal irritation. The cerebrospinal fluid contained 245 leukocytes, 68% of which were neutrophils. Right-lower-facial weakness and paresis of the right leg developed. After 12 months, he still had residual paralysis of the right foot necessitating orthopedic care.

Since measures such as administration of gamma globulin or vaccination directed against polioviruses cannot be expected to prevent infection with other enteroviruses, Hammon and his colleagues obtained evidence that other Coxsackie (and also ECHO) viruses actually might cause paralysis by studying cases regarded as protection "failures" during past field trials. Coxsackie viruses incriminated through documentation of the temporal relationship mentioned above were A7, B3 and B4. Steigman has presented evidence which suggests that types B2 and B5 may also produce paralytic disease. If B viruses do possess this capacity, it is somewhat surprising, although perhaps not inconsistent, that paralysis

was not noted during the many epidemics of aseptic meningitis described in the preceding section.

Acute Myocarditis

The most serious illness thus far attributable to Coxsackie viruses, and one which to some extent parallels the predilection of these agents to infect muscle in newborn mice, is acute myocarditis neonatorum (2). Primary or idiopathic myocarditis has been recognized for many years, and as early as 1952 it was suggested by German investigators that Coxsackie viruses might be responsible for some cases of "epidemic myocarditis of infancy." In that same year, in Johannesburg, South Africa, coincident with an epidemic of pleurodynia in the community, an outbreak of myocarditis occurred in a nursing home. Six of 10 affected babies died of fulminating illness with circulatory collapse. Coxsackie B3 was recovered from the feces of an infant who survived. Material from the brains of 2 babies who died induced lesions in suckling mice consistent with Group B infection. Continuing these studies, Gear and associates isolated B2 and B4 viruses from subsequent fatal cases.

In 1955, during an outbreak of "summer grippe" in Amsterdam which involved mostly adults, 5 fatal cases of myocarditis in newborn infants were studied by Van Creveld and DeJager. B4 virus was recovered from the heart muscle in all 5 cases; 3 also had meningoencephalitis. The same type of virus was isolated from fecal specimens of people in the community who were ill during the same summer period, 2 with pleurodynia and 1 with aseptic meningitis. Three of the mothers of the infants who died had influenza-like illness just before or after delivery. Kibrick and Benirschke recovered B3 virus from a fatal case with myocarditis and meningoencephalitis in Boston, and suggested that the infection was acquired transplacentally. The mother noted upper respiratory symptoms 2 days before a cesarean section; an overt illness developed in the infant on the third day of life and he died on the seventh. Delaney and Fukunaga in Hawaii have presented more definite evidence relating illness in the mother to infection in the infant. The mother delivered an apparently normal infant 3 days after the onset of aseptic meningitis. Fever developed 48 hours

postpartum and the child died on the eighth day of life. Coxsackie Group B, type 5 virus was recovered from the mother's stool, throat washings and spinal fluid, and from the infant's brain and heart. Jack has reported the isolation of B2, B3 and B4 viruses from the hearts of neonatal infants with myocarditis in Australia.

Additional clinical, epidemiologic and pathologic data have been contributed recently by South African investigators (24) following two outbreaks in a Cape Town maternity home in 1957. Coxsackie B3 virus was isolated from the myocardium of 4 fatal cases and from the stools of 6 other infants. The virus titers in the myocardium were high, and there appeared to be a relationship between virus concentration, the duration of the illness and the acuteness of the lesion. The cases of myocarditis occurred during an epidemic of Coxsackie disease, and infections were introduced into the nursery on both occasions by the admission of a pregnant mother during the incubation period of pleurodynia. Intrauterine infection was excluded in 7 of the 9 clinical cases, for the mothers showed no evidence of virus excretion or antibody production. The susceptibility of the very young is indicated by the observation that only those infants born after the first case in each outbreak became ill or infected, although all children in the nursery were cared for under the same conditions.

With the exception of a nonfatal case in a 5-year-old boy in Ohio shown to have B2 virus in his feces, the reported cases have been in newborn infants. Most of the deaths have occurred in the first week to 10 days of life. Whether similar factors are responsible for the susceptibility of the newborn human and that of infant mice and hamsters is not known. It is of interest that investigators in the Netherlands have demonstrated that a Coxsackie B virus which produced only a febrile reaction without signs of illness in adult monkeys produced fatal myocarditis in a newborn monkey. The data accumulated to date prompt the question of whether or not expectant mothers near term during epidemics of "summer grippe," pleurodynia or aseptic meningitis should be given large doses of gamma globulin. The question must remain unanswered until more is learned of the protective effect of gamma globulin in Coxsackie infections.

Clinically, infants with myocarditis progress rapidly from an apparent state of health to death in a state of shock. The first in-

dication of illness may be fever, lethargy and a failure to take feedings well. Inflammation of the throat may be noted initially. Then follow dyspnea, tachycardia, paleness, coughing and cyanosis, symptoms suggestive of pneumonia or neonatal sepsis. Hepatomegaly and signs of decompensation become evident before the blood pressure falls. Electrocardiograms have shown changes consistent with myocardial damage. Leukocyte counts have ranged from 10,000 to 25,000. If meningoencephalitis is also present, there will be cerebrospinal fluid pleocytosis.

Benign Pericarditis

In the past, pericardial friction rubs have been heard in patients with pleurodynia, but pericarditis has been a rare complication. Since 1957, four cases of acute pericarditis (three young adults in their twenties and one 74-year-old male) have been related temporally to Coxsackie B infections. One patient, a young man, had a bloody pericardial effusion, and a pericardial biopsy showed an organizing, hemorrhagic exudate and a chronic inflammatory cellular infiltration on the two sides of the pericardium. No agent was recovered from the pericardial tissue. In addition to fever and other constitutional symptoms, the patients complained of pain in the anterior aspect of the chest, aggravated by breathing and by assumption of the supine position. Pericarditis was manifest by a friction rub and inversion of T waves in the electrocardiogram. Although an arrhythmia persisted for 2 months in one case, all four recovered. Additional observations are needed to establish the natural history, as well as the validity, of Coxsackie pericarditis.

ECHO VIRUS DISEASES

Aseptic Meningitis

Advances in the field of virus diseases rapidly altered the status of the ECHO viruses by establishing etiologic associations for many of the types. This is particularly true in the case of aseptic meningitis, for, while isolation of a ubiquitous virus from the respiratory or gastrointestinal tracts does not relate it necessarily

to disease, the demonstration of a virus in the cerebrospinal fluid convincingly documents its relationship to the symptoms observed. There is now abundant evidence that ECHO viruses, like other enteroviruses, invade the central nervous system.

ECHO type 6 was isolated from cases in Rhode Island in 1954, and in New York in 1955 (13). Subsequent epidemics due to type 6 have occurred in Massachusetts, Washington, D. C. and Europe. Strains of two other types, 4 and 9, have been responsible for other major outbreaks of aseptic meningitis in North America and Europe and, in all, 13 different types have been associated with this syndrome.

Type 4 virus produced epidemics in Iowa in 1955 (14), in Sweden in 1956 and in South Africa in 1957. In the Iowa epidemic, it is estimated that 16% of the population of Marshalltown was involved. The 0-14 year age group experienced the highest attack rate—31%; those 60 and over, the lowest—5%. Fifty-five per cent of the patients had meningeal symptoms; 45% experienced a nonspecific "summer grippe" type of illness. The occurrence of both these illnesses at the same time, the similarity of the age-specific attack rates and the virus isolation and antibody studies incriminated the ECHO virus as a cause of minor febrile illness as well as of meningitis. Multiple cases occurred in 36% of the families in which there was illness; 50% of the secondary cases appeared by the fifth day.

ECHO 9 has produced the greatest number of outbreaks since it was recognized in 1956 as the cause of "Trent Valley Fever" or "Nottingham Meningitis." The presence of a rash (see below) in many of the patients with meningitis attracted particular attention to epidemics in Britain, Italy and western Europe. During the summer of 1957, there was widespread dissemination of type 9 virus throughout eastern Canada and the Middle West in the United States. It has been estimated that 40,000 cases occurred in the Milwaukee area and 200,000 cases in the Minneapolis-St. Paul area. During the 1956 type 9 epidemic in Belgium, the 114 cases studied fell into four groups. Forty infants and 11 adults had a pronounced meningeal syndrome associated with an eruption midway between scarlet fever and measles. Thirty-seven children and 8 adults had a mild meningeal syndrome. Twelve children had an influenza-like illness with rash and 6 children had a mild

febrile illness. Descriptions of epidemics in England and Scotland provided similar data.

Thus, during outbreaks of disease due to types 4, 6 and 9, and probably others, ECHO viruses spread widely in susceptible populations. Multiple infections in households are common, and there is a wide spectrum of clinical manifestations ranging from minor illness to meningitis. As in the case of Coxsackie viruses, the minor illness consists usually of low-grade fever, headache, nausea, mild sore throat, myalgia and irritability, lasts 2-3 days, and cannot be distinguished clinically, in the absence of a rash, from similar "summer grippe" illnesses due to other viruses.

Except for variability as to the presence of a rash (see below) the manifestations of ECHO meningitis are the same regardless of type. Further, this illness cannot be distinguished clinically from meningitis caused by Coxsackie or other viruses. The onset may be insidious, and the occurrence of a biphasic course has been noted; this does not seem to be as common a feature as in children with poliomyelitis. Usually, the onset is abrupt with the appearance of three major features: headache, vomiting and fever. The headache is frontal or retrobulbar, described as across the forehead or behind the eyes. Nausea and vomiting, sometimes incessant, last for 2-3 days. Temperatures vary from 99 to 105F., but most fall in the moderate range of 101 to 103. Nearly all patients complain of stiff neck and back; 20-50% have myalgia involving the legs. Young children, especially, complain of abdominal pain. Ten to 15% of patients have various complaints such as photophobia, drowsiness, giddiness and mild sore throat.

Examination confirms the stiffness of the neck and back and, when it is present, reveals the exanthem described in the next section. Pharyngeal lymphoid hyperplasia may be present, and in a few patients infected with types 9 and 16, an enanthem occurs. This consists of small, yellowish or grayish white lesions on the tonsillar pillars or buccal mucosa. Muscular tenderness, usually of the extremities, is present in some patients, and in a few cases transitory muscle weakness has been noted (see below).

The peripheral leukocyte count is usually normal, although as with Coxsackie B virus meningitis, elevations to 15,000 have been reported. Cerebrospinal fluid cell counts have ranged from 5 to 2,500 cells, but are usually below 500. Polymorphonuclear cells

may predominate early in the illness; later, lymphocytes predominate. A slight elevation of protein occurs in about one half of the cases; sugar and chloride values remain normal.

The initial severity of the illness is in contrast with the subsequent benign course. The fever persists for 2-15 days, with an average duration of 4-9 days. In some outbreaks, a tendency to relapse, with 5-10 days between recurrences, has been reported. A few patients experience slow recovery associated with tiredness and mild depression.

ECHO Exanthem

To date, rash has been noted in infections with ECHO virus types 2, 4, 6, 9, 14 and 16. Rash also has been observed with Coxsackie A9 and A16 infections. An exanthem has been reported most frequently in association with meningitis due to ECHO 9 (18), occurring in from 10 to 50% of patients in the different epidemics. In one epidemic, rash occurred in 100% of children under 3 years of age and in 45% of those 5-15 years. The rash may appear from the first to sixth day of illness, but characteristically appears by the third day shortly after the onset of or during the course of the fever. It consists of small, pink, discrete macules or maculopapules resembling those seen in German measles or in mild measles. The face is almost always involved, and the rubelliform rash usually spreads to the neck, shoulders, trunk and sometimes to the extremities. Occasionally, the spots on the face become semiconfluent and of a violaceous tint; in this event, the rash resembles that of erythema infectiosum or "fifth disease." In some patients, the rash is petechial, causing these cases to simulate meningococcemia.

In contradistinction to the rash of type 9 disease, the exanthem produced by type 16 virus appears after fever and other acute symptoms have subsided. Viruses subsequently classified as type 16 strains were first isolated by Neva and Enders from patients with a rubella-like exanthem during an epidemic in Boston in the summer of 1951. The newly recognized entity was named "Boston exanthem." In 1954, Neva isolated similar strains from cases in Pittsburgh (15). None of these cases had meningitis, but the epidemic pattern closely resembled that described above. In infants,

the first evidence of illness is irritability and fever. Older children have temperatures of 101-103F., and complain of headache, mild sore throat and anorexia. The disease is symptomatically more severe in adults. In them, the onset is abrupt, initial symptoms being chills, headache and muscle aches and pains. They commonly complain of burning or pain in the eyes and, less commonly, of sore throat and crampy abdominal pain. Nearly all children have an exanthem; rash is a much less constant finding in adults, and is scanty when present. In most cases, the rash appears within several hours to a day after the fever and other signs and symptoms subside. The rash in children is often generalized, with the main distribution over the face, chest and back and, to a lesser extent, buttocks and extremities. It is similar to that produced by other ECHO types. The lesions are pink, not as dark as those of measles, and slightly raised to present a pebbled appearance. An occasional patient also has mucous membrane lesions. An enanthem consisting of small ulcerations on the soft palate or uvula, without vesicles or ulcers, has also been noted. Whether either or both of these types of enanthem are due to type 16 is not definite, although the latter resembles that seen in ECHO 9 infections. There is no significant adenopathy.

Clinical differentiation of ECHO exanthem from other epidemic exanthemata may be difficult, but certain features are of help. Measles and rubella occur most commonly in the winter and spring months; ECHO epidemics occur in the summer. Both measles and rubella have long incubation periods. Measles can be more easily excluded than rubella because of the absence of Koplik's spots, the character of the skin eruption and the brief duration. The helpful feature in excluding rubella is the absence of the characteristic lymphadenopathy, particularly posterior cervical and occipital. Roseola infantum differs in that its degree and duration of pre-eruptive fever are greater, its communicability is low, and nearly all cases occur in children under 3 years of age. The necessity for distinguishing the petechial form of ECHO rash from meningococcemia, particularly when meningitis is also present, has been referred to above. In view of the danger of delaying treatment in meningococcal disease, it is recommended that sulfonamide therapy be given in such cases until a specific diagnosis can be made.

Paralytic Disease

Definition of the role of ECHO viruses in the causation of paralytic disease faces the same problems as in the case of Coxsackie viruses. As yet, the ability of ECHO types to produce paralysis in humans has not been conclusively established, but evidence that they occasionally may do so is accumulating gradually. Steigman (23) has reported the case of a 28-month-old girl hospitalized in 1952 with meningitis. Within 48 hours weakness of both lower extremities and of the diaphragm and intercostal muscles developed. A macular rash was noted on her chest and abdomen. The patient died of progressive bulbospinal disease, and the nervous system showed lesions similar in distribution and character to those associated with poliovirus. ECHO virus type 2 was isolated from the spinal cord; no evidence was obtained of poliovirus infection.

During the 1954 outbreak of type 6 infection in Massachusetts, Kibrick and associates observed spotty, asymmetrical paralysis with gradual improvement in 22 patients. The muscles most frequently involved were the gluteus medius, hip adductors and, occasionally, the gastrocnemius. In none of the patients did increases in titer of poliovirus antibody develop. Karzon, *et al.* (13) reported the finding of transient muscle weakness during the 1955 type 6 epidemic in New York State. An additional type 6 case with paralysis has been reported in Sweden by Svedmyr.

During the type 4 epidemic in Iowa, there were two cases in which a minor transient weakness of one leg was noted. During a family outbreak in Switzerland due to type 4, paralysis of the right leg and weakness of the right arm developed in an adult. From the gamma globulin field trials, Hammon found two presumptive cases, one related to type 4 and the other to type 16.

During the type 9 epidemic in Belgium, Nichol and associates observed 5 patients in whom meningitis was accompanied by myelitis and paralysis of the palate or of the leg. Concomitant presence of poliovirus was not proved, nor was there definite proof of its absence. Sabin has reported that among patients infected with type 9 in Milwaukee in 1957, one had mild bulbar disease and another spinal paralysis. Finally, Verlinde recovered a type 9 strain from the brain of an infant with encephalitis. It is

of interest that this strain, in contrast to types 4 and 6 tested in chimpanzees by Itoh and Melnick, produced lesions in monkeys difficult to distinguish from poliovirus infection.

What percentage of persons infected with ECHO—or with Coxsackie—viruses develops permanent paralysis? An answer to this question awaits further study, but it is apparent that such paralysis has been a rare finding in the many epidemics reported. The answer is of practical importance, for paralysis due to other enteroviruses must be recognized in the evaluation of widespread poliomyelitis vaccination. With the exception of ECHO exanthem, no distinctive clinical features of nonpoliovirus paralysis have emerged. The following specimens should be submitted to local or state laboratories for diagnostic purposes: pharyngeal swab in broth, stool specimen or rectal swab, cerebrospinal fluid, acute- and convalescent-phase serum specimens. Directions for the collection and shipment of specimens are distributed by the various diagnostic laboratories.

Summer Diarrhea

Some of the first ECHO viruses were isolated by Ramos-Alvarez and Sabin (19) from children with summer diarrhea. Other enteroviruses were recovered also, but ECHO viruses, belonging to 13 different types, were the most frequent. Their incidence was 6 times greater in the diarrheal group than in a control group. At the same time, enteropathogenic *E. coli* were also found with higher frequency in the diarrheal than in the control group. It was concluded that summer diarrhea in very young children is not a clinical entity but rather a consequence of transitory infections with a variety of viruses and bacteria.

Strong evidence in support of the etiologic role of type 18 was obtained by Eichenwald *et al.* (7) from a study of an outbreak of diarrhea in a nursery for prematures. Evidence of infection with type 18 virus was found in every infant with diarrhea, but not in those who remained well. The virus was present only during the epidemic; the development of type 18 antibodies was temporally

related to the occurrence of diarrhea. A second outbreak occurred among infants on another ward in the same hospital after exposure to a nurse known to be excreting ECHO 18.

Clinically, the type 18 disease was mild. There was no significant temperature elevations or hypothermia. The diarrhea persited from 1 to 5 days, with a mean duration of 3 days. Most of the infants passed five or six watery, greenish stools each day. Treatment consisted of reduction in caloric content of feedings, parenteral hydration when indicated, and gradual return to normal formulas. There were no recurrences.

There is as yet no evidence that ECHO viruses produce diarrhea in older children and adults.

Respiratory Illness

A heretofore unrecognized ECHO virus, designated type 20, was isolated by Rosen and associates from infants newly admitted to an orphanage in Washington, D. C. In some instances, isolation and antibody studies established a close association between the onset of illness and presence of the virus. Certain of these illnesses were characterized by fever of 2 days' duration, and both respiratory and gastrointestinal symptoms. However, comparable fevers were equally prevalent in other nursery children, and similar illnesses were common in children from whom no viral agent was recovered. Therefore, it could not be determined that the cold-like symptoms were actually due to infection with ECHO type 20 virus.

There is evidence to suggest that certain strains classified as type 10 may be related to respiratory disease. ECHO 10 viruses are an antigenically heterogeneous group with some properties that distinguish them from other ECHO viruses. Type 10 strains have been isolated from healthy children, from children in Cincinnati with diarrheal disease and from Washington orphanage children with a variety of symptoms. Sabin isolated type 10 strains from the stools of chimpanzees who experienced an outbreak of coryza. Antibodies for the virus appeared during convalescence.

Nasal instillation of tissue cultures reproduced the coryzal syndrome in other chimpanzees. These results prompted the description "chimp rhinitis" virus. Ramos-Alvarez and Sabin demonstrated that only 10% of children aged 1-5 had type 10 antibody in contrast to 63% of medical students. Most recently, a preliminary report from Sweden has linked ECHO 11 with croup and the production of colds in adults. The role of types 10 and 11 in the production of respiratory disease has yet to be defined.

ADENOVIRUS DISEASES

Acute respiratory infections constitute the commonest cause of illness, and it is encouraging that intensive research by many investigators has resulted in the isolation of a number of new viral agents from the respiratory tract. (Tables 2 and 3). As with the

TABLE 2.—ADENOVIRUSES AND DISEASE*

TYPES	ASSOCIATED DISEASE
3, 4, 7, 14	Acute respiratory disease (ARD)
	Pneumonia
7a	In infants
3, *4*, *7*, 14	In adults with ARD
1, 2, *3*, 4, 5, 6, 7a, 9, 14	Pharyngitis and pharyngoconjunctival fever
2, *3*, 4, 6, *7a*, 9, 10, 15	Follicular conjunctivitis
3, 7a, *8*	Epidemic keratoconjunctivitis (EKC)

*Types most often related to a particular manifestation are in italics.

enteroviruses, certain of these respiratory viruses were promptly identified as the cause of clinical syndromes; others have been shown to infect man but the frequency with which they produce clinical manifestations remains to be established; still others have yet to be related definitely to disease. The adenoviruses comprise a group of agents possessing a common complement-fixing antigen, the group being separable into different types through the

use of specific neutralizing antisera. Eighteen human types have been classified, and others are under study. Five different types have been isolated from monkeys and chimpanzees, but man appears to be the only reservoir for types causing human disease. Adenovirus infections probably occur throughout the world; infection, as reflected by the presence of antibody, is common. By the age of 5, over 80% of children have antibody to at least one type, and 50% have antibodies to two or more types.

The adenoviruses were first reported in 1953 by Rowe and coworkers, who observed that cellular outgrowths of fragments of human adenoids underwent spontaneous degeneration after prolonged incubation in tissue culture. A number of strains, principally types 1, 2, 5 and 6 have since been obtained from cultures of both tonsils and adenoids. Fifty per cent of children may harbor one of these types, the virus being present as a so-called "latent" agent within the lymphoid tissues of the pharynx. The individual has antibodies for the infecting type but has no symptoms and is not infectious at this stage; how frequently the initial stage of infection with these types in children is accompanied by symptoms is still under study. Longitudinal study of children born into a population of Cleveland families showed that types 1 and 2, and to a lesser extent type 6, infect many children and that by the age of 5 the percentage of children with antibodies for these types was the same as in the adult groups. Despite this fact, few of the many respiratory illnesses experienced by this population during a winter season could be attributed to adenovirus infections. From epidemiologic studies done in the Washington, D. C. orphange mentioned above, Huebner *et al.* concluded that one half of childhood adenovirus infections result in a febrile illness. Ginsberg *et al.* have shown that types 1, 2, 5 and 6—those types which infect early and persist in tonsils and adenoids—differ in a number of biologic properties from types 3, 4 and 7—types which produce epidemic disease later in life. It has been hypothesized that differences in the biologic characteristics of members of the adenovirus group may in part account for the different behavior of these viruses in man.

The clinical importance of types associated with epidemic disease was more readily determined. In 1954, almost simultaneous with the discovery of latent adenoviruses, Hilleman and Werner

isolated an agent, now classified as type 4, from army recruits sick with a grippe-like illness. This disease, variously termed catarrhal fever, febrile catarrh and acute respiratory disease of recruits (ARD), had been previously recognized as an important problem in military forces. During World War II, volunteer experiments performed by the Commission on Acute Respiratory Diseases, indicated that ARD was a distinct clinical entity caused by a virus. Hilleman and Werner demonstrated increases in titer of type 4 antibody in their current cases; retrospective studies by Dingle and associates then showed that an immunologically related virus had been transmitted to the volunteers. It has now been shown that types 7 and 14, and sometimes type 3, also produce ARD in military recruits.

Two other epidemic diseases, pharyngoconjunctival fever and keratoconjunctivitis have been related to types 3 and 8, respectively. Huebner and his associates were the first to demonstrate that type 3 virus is a frequent cause of nonbacterial pharyngitis with or without conjunctivitis. Jawetz *et al.* have accumulated data which indicate that type 8 adenovirus is the causative agent of keratoconjunctivitis. A number of investigators have isolated many different strains from cases of follicular conjunctivitis.

Thus, adenovirus infections result in catarrhal inflammation of the mucous membranes of the respiratory or ocular system, or both. As suggested by the name, infection is accompanied by involvement of the regional lymphoid tissues. There is considerable overlapping in the syndromes produced, for one type of virus may cause an illness resembling ARD in one patient and conjunctivitis in another. Such variation is particularly true in sporadic cases; during epidemics, the clinical picture usually is more consistent.

Acute Respiratory Disease (ARD)

This disease, peculiarly and for reasons unknown, occurs predominantly in military recruits (8). It behaves somewhat like influenza, both clinically and epidemiologically. During the winter months, 80% of recruits may be infected; 20-40% will be sufficiently ill to require hospitalization and another 20% may need dispensary care.

In volunteers given respiratory tract secretions, the incubation

period was 5-6 days. Volunteers injected intramuscularly with a pool of types 3, 4 and 7 developed symptoms 2-3 days post-inoculation. In contrast to influenza, the onset is usually gradual over a period of 2-3 days. It may, however, be abrupt, and the individual case cannot be distinguished clinically from influenza, or indeed from febrile respiratory illnesses caused by other viruses. The major symptoms are fever and chilliness, usually accompanied by headache, malaise and anorexia. In general, symptoms referable to the respiratory tract are less common than the constitutional symptoms. Coryza, sore throat, hoarseness and dry cough are common, but are generally mild in degree.

Examination shows an acutely ill patient, and often little else. About one half of the patients have nasal obstruction and pharyngeal injection with lymphoid hyperplasia. About 10% have mild cervical lymphadenopathy. Curiously, conjunctivitis is infrequent. During epidemics, 10-15% of patients have pulmonary rales and x-ray evidence of pneumonia. Total and differential leukocyte counts are normal. Cultures of the throat yield normal bacterial flora. The febrile course varies from 2 to 4 days, and the temperature may reach a peak of 103-104 F. The usual range is from 100 to 102, the fever subsiding either abruptly or by lysis. When present, symptoms referable to the respiratory tract may persist for a week or more. Bacterial complications are extremely rare, and recovery is uneventful. There is no need for prophylactic use of antibiotics. As in other virus infections, symptomatic and supportive care is the basis of therapy. Prevention of this disease in military recruits has been accomplished by using vaccine containing two or three of the epidemic types (3, 4 and 7). Studies by a number of investigators using killed vaccines have demonstrated reductions of from 72 to 98% in attack rates of adenovirus infections at military installations. Use of adenovirus vaccine, accordingly, has been adopted by the armed forces.

It is emphasized that ARD appears to be almost exclusively a disease of military recruits. Many studies of civilian populations have consistently found that adenoviruses cause only 0.5-3.0% of respiratory illnesses suffered by families, college students and adults. Types 4 and 7 have been isolated from sporadic infections,

and two civilian outbreaks of illness due to type 7, one in England and one in Canada, have been reported. Very few strains of type 4 have been isolated from civilians, and to date this type has been associated with but one epidemic. Van der Veen and Ploeg isolated type 4 from 11 patients (and type 3 from 46 patients) ill during a localized epidemic of pharyngoconjunctival fever in the Netherlands in 1957. The low incidence of adenovirus infections in civilian populations does not justify vaccination of the general public (12). As noted below, use of a properly constituted vaccine may be desirable in certain special situations. A commercial vaccine now being promoted for general use in civilian populations does not include the types which most commonly infect civilians. Use of such a vaccine for civilians is not recommended.

Pneumonia

In adults, adenovirus pneumonia has been observed almost exclusively in military recruits in association with ARD. Cases with pneumonitis generally have a higher and more persistent febrile response. In addition to the constitutional features of ARD, fine crepitant rales are audible. Roentgenograms show peribronchial infiltration, most marked in the bases. The illness thus resembles a mild case of primary atypical pneumonia, and is distinguished from it only because cold hemagglutinins and streptococcus MG agglutinins do not develop.

In infants, there is evidence which suggests that adenoviruses may produce a severe, even fatal, pneumonia. During an outbreak of type 7a infections in a pediatric ward in Paris, Chany *et al.* (3) observed 12 cases of virus pneumonia, 2 of which were fatal. Type 7a virus was isolated from the spinal fluid—tested before death because of a picture of encephalitis—lungs, and brain of one of these, a 12-month-old child. Two other fatal cases occurred during the same 4-month period, but were not tested for evidence of adenovirus infection. Three months later, virus was recovered from a 4½-year-old child who developed a fatal pneumonia during a family epidemic due to type 7a. All the cases attributed to this agent had red throats and signs of pneumonia. Other features noted in some cases were conjunctival injection, a morbiliform

rash, meningismus, encephalitis and diarrhea. These four fatal cases and four others collected in a prior period showed similar pathologic lesions; necrosis of tracheal and bronchial epithelium and acidophilic necrosis of pulmonary parenchyma. A most important finding was the demonstration of intranuclear inclusions in the epithelial cells of the bronchi and alveoli. The cytologic changes noted were quite similar both to those described in adenovirus-infected cells in culture and to those lesions reported in children by Goodpasture and associates in virus pneumonias following measles and pertussis. Since these infant deaths are the only fatalities attributed to adenovirus infection, confirmation and extension of the observation of the French investigators is of considerable importance.

Pharyngitis and Pharyngoconjunctival Fever

Adenovirus infections causing pharyngitis, with or without conjunctivitis, occur sporadically in both military and civilian populations. Sporadic cases due to many types have now been reported, and there appears to be no significant clinical differences relative to type. Most sporadic cases yield types 1, 2, 3 and 5, and it has been suggested that conjunctivitis is seen less often with these endemic infections than during epidemics. Adenovirus epidemics in civilian populations occur chiefly in children during the summer months. Most of the outbreaks have been associated with summer schools or camps, and many have been linked with swimming. Most of these epidemics have been due to type 3. Bell *et al.* have reported an attack rate as high as 70% in a children's camp. The secondary attack rate in young children in family outbreaks is about 50%. In a number of studies, principally those involving camps and swimming, males have been more frequently attacked than females. Since evidence has been presented to suggest that conjunctival irritation favors induction of infection, this has been offered as one explanation for the sex difference. The presumption is that the boys, being less lady-like, not only swim more but rub their eyes harder. Type 3 adenovirus is inactivated by the same amount of free chlorine required to destroy *E. coli* and *S. typhosa,* and is thus more sensitive to chlorination than poliovirus or Coxsackie virus. Epidemics may be related to swimming pools

not as a result of contaminated water but because of the intimate contact and conjunctival irritation associated with swimming.

The clinical manifestations of adenovirus pharyngitis are similar to those of ARD with the addition of more pronounced inflammation of the throat and, in some cases, of the eye. The triad of fever, pharyngitis and conjunctivitis constitutes pharyngoconjunctival fever (1). The incubation period is 5 or 6 days, with a gradual onset in most cases. Other symptoms include chilliness, headache, anorexia, scratchy throat and cough. Symptoms referable to the lower respiratory tract are said to occur more often in sporadic cases during the winter months and to be less common during summer outbreaks. Nasal obstruction may occur and epistaxis has been described. Gastrointestinal symptoms have been infrequently noted in North American epidemics; in several European epidemics nausea, vomiting and diarrhea, singly or in combination, were present in up to one third of the patients.

Examination shows an acutely ill patient who may have unilateral or bilateral follicular conjunctivitis. The pharynx is moderately red and cobblestoned with hyperplastic lymphoid tissue. Pinpoint patches of grayish white exudate may be present on this tissue and the tonsils. In contrast to streptococcal pharyngitis, enlargement and tenderness of cervical nodes is moderate. Patients with conjunctivitis have preauricular lymphadenopathy. Total and differential leukocyte counts are usually normal; neutrophilia may be seen with counts as high as 12,000. Throat cultures yield normal bacterial flora. Adenoviruses may be isolated from the throat, the inflamed conjunctivæ and from the stool. The febrile course varies from 3 to 5 days; the average peak of temperature is between 101 and 102 F.; fever subsides by lysis. Complications are uncommon, although otitis media and residual corneal opacities have been reported. Details regarding the eyes are presented in the next section. In the absence of conjunctivitis, it may be difficult to distinguish individual cases from the nonspecific febrile illnesses produced in the summer by the enteroviruses. In herpangina, which is also common in children, lymphoid hyperplasia is rare and the herpetiform lesions are seen on the palate and anterior pillars. Without laboratory studies, few of the sporadic illnesses during winter months can be distinguished from other virus respiratory infections. At present, as a guide to therapy, it is nec-

essary only that all these illnesses be distinguished from bacterial infections, particularly streptococcal pharyngitis. Such differentiation is best accomplished by use of throat cultures and leukocyte counts.

It has been suggested that adenovirus vaccine containing type 3 virus be used to prevent epidemics of pharyngoconjunctival fever in children's institutions and summer camps. Additional experimental data must be collected before the indication for vaccination of civilian groups can be determined.

Follicular Conjunctivitis

Acute follicular conjunctivitis (25) similar to that seen during epidemics of pharyngitis, may occur as the only manifestation of adenovirus infection. Conjunctivitis without systemic manifestations apparently is most common among persons in the older age groups. The incubation period in volunteers was 2-7 days. The illness begins as a unilateral, nonpurulent inflammation of both palpebral and bulbar conjunctivæ. Involvement may be monocular or binocular, one eye often being affected some days before the other. The most common symptoms are itching, burning, irritation and foreign body sensation. Photophobia has been noted, but is seldom severe.

Examination shows excess lacrimation, serous exudation, hyperemia, blepharospasm, hyperplasia of palpebral lymph follicles and enlargement of preauricular lymph nodes. Subconjunctival hemorrhage and periorbital edema may occur. Corneal changes are rare, but have been described, particularly by Canadian investigators, as follows: transient stromal opacities appearing after the eighth day and fading within 6 weeks; opacities resembling those of keratoconjunctivitis but persisting for only 6 months; diffuse stromal edema which reduced vision for 3 months after subsidence of the acute phase. Inclusion bodies do not occur. Antibiotics have no effect on the course of the disease. The illness is self-limited and usually clears in a week. It occasionally persists for as long as 3 weeks. Treatment with topical cortisone or hydrocortisone produces abatement of symptoms and signs, but use of steroids should be restricted to avoid producing exacerbation of a misdiagnosed herpes simplex keratitis.

Epidemic Keratoconjunctivitis (EKC)

Epidemic keratoconjunctivitis (EKC) (25) is most prevalent in the Orient. It was first recognized in the United States in 1941, and was thought to have been imported from the Far East by way of Hawaii. During World War II, it was seen chiefly in workers in shipyards and industrial plants exposed to arc welding and eye injuries. Recent epidemics have been reported in Italy, Germany and Scotland. In the United States and Canada, outbreaks have been traced to contamination of instruments, particularly tonometers, used in eye clinics. In 1955, Jawetz and associates isolated an adenovirus, classified as type 8, from a patient with severe keratoconjunctivitis. Subsequent studies have indicated a significant association between this virus and the disease in various parts of the world. Most patients with adequate paired serum specimens develop an increase in titer of type 8 neutralizing antibodies. Ninety-five per cent of sera from patients in Japan, Italy, Switzerland and North America with EKC contain type 8 antibody, whereas only 7% of matched controls have such antibody. EKC is now regarded as being caused almost entirely by type 8, although sporadic cases have been associated with other types. Mitsui and his associates in Japan, and Bietti and Bruna in Italy, reproduced the disease in volunteers by scraping the conjunctiva and dropping type 8 virus grown in tissue culture into the conjunctival sac. Incubation periods ranged from 5 to 8 days. The initial clinical manifestations are similar to those of follicular conjunctivitis: foreign body sensation, burning, tearing, hyperemia, chemosis and enlargement of follicles and preauricular nodes. A serous or seromucoid exudate forms, and a pseudomembrane may appear. The onset of keratitis is marked by pain, photophobia and blurring of vision. Corneal changes develop 7-10 days after onset of the conjunctivitis, 2-3 days after about 50% of patients have experienced involvement of the other eye. The lesions may initially resemble a superficial punctate keratitis, but the more serious feature is the appearance of subepithelial, grayish, disk-like foci beneath Bowman's membrane. The disks become circumscribed and show a tendency to coalesce only in exceptional cases. Japanese investigators have reported an incidence of keratitis ranging from 35 to 60%; Mitsui states that keratitis is uncommon

in the infantile form of EKC. Most opacities disappear after 6 months. In 1-10% of patients, permanent corneal opacities may result in impairment of vision.

To prevent keratitis during a hospital epidemic, Leopold injected a total of 20 cc. of convalescent serum within the first 4 days of disease. One of 6 people so treated developed corneal opacities; 8 of 11 untreated patients developed opacities. A hazard of this therapy is illustrated by the development of hepatitis in one of the recipients of serum. Type 8 antibody is infrequent in the general population and, therefore, ordinary immune globulin would contain a negligible amount of such antibody. Additional studies are necessary to determine the effectiveness of hyperimmune serum or specially processed gamma globulin in the prevention of keratitis. Insufficient data are available regarding topical steroid therapy.

OTHER RESPIRATORY VIRUSES

Since 1952, the continuing effort to delineate the etiology of the common respiratory diseases has resulted in the identification of at least 8 other viral agents. Although sufficient time has not yet elapsed to permit adequate definition of the importance of these viruses in human disease, a number have been included in experimental "cold vaccines." Accordingly, physicians soon will be hearing more about the viruses listed in Table 3.

Sendai, CA and HA viruses are myxoviruses. Viruses of this group share properties such as affinity for certain mucins, and the adsorption to, hemagglutination of, and elution from erythrocytes. Influenza A and B, mumps and Newcastle disease viruses are also myxoviruses. Sendai, CA and HA viruses are more like the latter two, and it has been suggested that they be renamed para-influenza viruses.

Sendai-HVJ-Influenza D

This agent was isolated in Sendai, Japan, during an outbreak of pneumonitis in a nursery for newborns. Eleven of 17 infants died with hyperemic lungs and hemorrhagic pneumonia. The virus hemagglutinates red cells, and has been referred to as Hemag-

TABLE 3.—New Respiratory Viruses

Virus	Associated Disease
Sendai (HVJ)	Newborn pneumonitis
or	
Influenza D	Epidemic influenza
CA	Croup
	Acute laryngotracheobronchitis
Hemadsorption viruses (HA)	
Type 1	Febrile respiratory illness in children
Type 2	Croup in children; coryza in adult volunteers
2060	Mild respiratory illness in recruits
	? Coryzal illness in adult volunteers
JH	Mild respiratory illness in children
	? Coryzal illness in adult volunteers
CCA	Chimpanzee coryza
	Inapparent infection in children
Coe	? "Pharyngitis" and "common cold" in soldiers

glutinating Virus of Japan (HVJ). Since it resembles influenza viruses, it was suggested that Sendai virus be classified as influenza D. In the United States, 40% of individuals, excepting children 6 months to 3 years of age, have antibody which reacts with this virus. Occasional antibody increases have been documented in the United States and Great Britain in patients with mild respiratory illness, influenza and pneumonia. Because of the antigenic relationships of Sendai with other myxoviruses, the significance of these antibody data is not clear. Sendai virus produced disease in adults resembling that due to influenza A and B viruses during an extensive outbreak in Vladivostok, Russia, in March, 1956.

Croup-Associated Virus (CA)

In 1952, Chanock (4) reported the isolation of this agent from 2 of 12 infants with croup in Cincinnati. CA virus also has the properties of a myxovirus. The infants from whom the viruses were isolated and 3 additional patients developed increases in antibody titer. Similar agents were isolated by Beale and associates in Toronto from 10 of 15 children with acute laryngotracheo-

bronchitis. Of 6 patients tested, all developed antibodies in convalescence. CA virus appears to be one of the etiologic agents responsible for the clinical syndrome of nonbacterial croup. Its capacity to produce disease in older children and adults is not known.

Hemadsorption Viruses (HA)

The hemadsorption viruses, so called because "adsorption-hemagglutination" occurs when appropriate erythrocytes are added to infected tissue cultures, were first isolated by Chanock *et al.* (6) from children with respiratory illnesses in the fall of 1957. Two serologic types have been identified. HA 1 was isolated from 35 children, 27 of whom were involved in an outbreak of febrile respiratory disease in Washington. In this instance, there was a significant association of virus isolations with febrile illnesses. In addition to fever of 2-3 days' duration and cough, nearly half of the cases had moist, medium-to-fine rales. HA 2 virus was isolated from 3 infants hospitalized with acute laryngotracheobronchitis. HA 2 was used as inoculum in 32 adult male volunteers. Eighteen developed clinical illness 6 days later, and 25 developed a rise in antibody titer for type 2 virus. The most common symptoms of the "cold-like" illness induced were nasal obstruction and discharge, sneezing and coughing. Less frequent were headache, sore throat, lacrimation and chilliness.

Preliminary surveys have shown that most young adults have antibodies for both types. The viruses are present throughout the year, but it is not yet known how often they produce symptoms. Chanock has reported that either HA 1 or HA 2 was isolated from 6% of 879 children with respiratory infections. In children, HA 2, the agent which produced "colds" in adults, seems to be more often associated with the croup syndrome than HA 1.

2060 Virus

In 1956, Pelon *et al.* (16) reported the isolation of this agent from a nasopharyngeal washing (No. 2060) obtained from a naval recruit with a mild respiratory illness in October, 1954. Increases in antibody titer were measured in 26% of men with respiratory illness in two recruit companies. Sera from a number of

Chicago children and gamma globulin neutralized the 2060 virus. In New Orleans, 50% of randomly selected sera contained antibody. The 2060 virus, like the related JH virus, is difficult to grow in the laboratory, and neutralizing antibody end-points are hard to measure. The significance of this agent as a cause of disease can be determined only when easier methods of isolation and more precise measurements are available.

JH Virus

Isolation of the JH (Johns Hopkins) virus was reported by Price (17) in 1956, who stated that the agent had been isolated from respiratory cases in all seasons of the year from both adults and children. About 20% of individuals over 8 years of age possessed neutralizing antibody. Price vaccinated a number of groups of children, and reported good results in one group which experienced an outbreak of respiratory disease which may have been caused by JH virus. Only 3 of 50 children given two doses of JH vaccine developed respiratory illness, whereas 23 of 50 children given placebo became ill. The symptoms noted were coryza, mild sore throat, slight fever (3 children had temperatures between 102 and 103 F.) and cough.

Immunologic studies have shown that 2060 and JH are closely related but not identical viruses. A number of other investigators have failed to isolate JH or 2060 viruses from nasal secretions of children or adults with coryzal illnesses. Volunteer experiments in Great Britain with JH virus and in the United States with both JH and 2060 viruses suggest that these agents may induce coryzal illnesses in adults. To date, however, the occurrence of colds in controls and the lack of correlation between clinical results and antibody responses have made the data difficult to interpret.

Chimpanzee Coryza Agent (CCA)

In 1955, Morris, Blount and Savage recovered this virus from 1 of 14 chimpanzees during an outbreak of illness characterized by coughing, sneezing and mucopurulent nasal discharge. All animals that had coryza developed specific antibody. When suscep-

tible chimpanzees were inoculated with CCA virus, coryza occurred after a 3-day incubation period. A person working with the infected chimpanzees experienced a coryzal illness and developed a rise in antibody for CCA virus. During a study of infants with laryngotracheobronchitis and pneumonia, Chanock and associates (5) isolated two agents which are indistinguishable from CCA virus. Since 80% of children possessed neutralizing antibody for this virus by the age of 4 years, it appeared that CCA infection was common among young children. When a group of children hospitalized with pneumonia and bronchiolitis was compared with a control group, the incidence of infection as determined by serologic tests was not significantly different. Infection, then, must have resulted in mild illness or none at all. It is of interest that among infants who were hospitalized, whether for respiratory disease or not, the rate of infection was 6 times greater (45%) than in the clinic population (7%). The role of CCA virus in disease and the significance of its apparent wide dissemination in the hospital remains to be determined.

Coe Virus

At the time of this writing, Coe virus (named for the patient) is the "newest" virus on the list. In November, 1958, Lennette *et al.* reported the recovery of 4 agents distinct from known viruses during the course of studies on respiratory disease at Fort Ord, California. The agents had similar properties and were considered to represent strains of a single virus. Two strains were recovered from patients hospitalized in 1954, and two from patients hospitalized in 1956. Three patients had "pharyngitis," one had a "common cold." Paired sera were available from 3 cases; an increase in titer of antibody against Coe virus developed in each. Three of 23 other selected patients showed increases in both neutralizing and complement-fixing antibody levels. Three fourths of the patients had no neutralizing antibody, suggesting that Coe virus is a relatively uncommon cause of disease. The sample tested was small, however, and additional studies must be done to determine the place of Coe virus in respiratory disease.

Other Recent Virus Isolations

Methods have been developed for the propagation of the viruses which cause such long-recognized clinical entities as measles, chickenpox, herpes zoster and cytomegalic inclusion disease (salivary gland virus). As a result, investigators are expanding knowledge of the epidemiology of all these diseases, and are actively engaged in attempts to produce a measles vaccine.

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